[b.] allowing said cell culture to live under conditions wherein said nucleic acid molecule is expressed in said cell culture.

45. (Added) The method of claim 44, wherein said animal cell culture is an insect cell culture or a mammalian cell culture.

46. (Added) The host cell of claim 8, wherein said host cell is a mammalian cell.

47. (Added) The mammalian cell of claim 46, wherein said mammalian cell is a human cell.

REMARKS

Applicants acknowledge, with appreciation, the Examiner's allowance of claims 2 and 3.

Applicants have cancelled claims 5 and 36-38 without prejudice and reserves the right to prosecute the subject matter of the cancelled claims in any future application claiming benefit or priority herefrom under 35 U.S.C. § 120.

Applicants acknowledge, with appreciation, the Examiner's statement that "[t]he existing 'comprising' language is acceptable with reference to nucleic acids encoding SEQ ID NO:4…." In view of that statement, applicants have amended claim 1 to recite a substantially purified nucleic acid comprising consecutive nucleotides that encode a human TRELL polypeptide, wherein said TRELL polypeptide comprises the amino acid sequence of SEQ ID NO:4. Claim 7, which depends from

claim 6, which in turn depends from claim 1, has been amended to recite that the nucleic acid comprises SEQ ID NO:3. Claims 1 and 7 have been amended to delete the recitation of SEQ ID NO. 2 and SEQ ID NO. 1, respectively.

Claim 4 has been amended to recite a substantially pure nucleic acid that hybridizes under stringent conditions to SEQ ID NO:3, wherein said stringent conditions comprise washing steps using 2X SSC, 0.1% SDS at 65°C, and wherein said nucleic acid encodes a TRELL polypeptide of SEQ ID NO:4, or a soluble fragment thereof, that is capable of binding to a cell selected from the group consisting of: a K562 promyelocytic cell; a THP-1 monocytic leukemia cell; an HT29 colon adenocarcinoma cell a 293 embryonic kidney cell; and a Cos kidney fibroblast cell.

Applicants have added claim 40, which recites a substantially pure nucleic acid, comprising consecutive nucleotides that encode a human TRELL polypeptide, wherein said nucleic acid comprises SEQ ID NO:3. Applicants have added claim 41, which depends from claim 4, and recites that the soluble fragment of said TRELL polypeptide comprises an amino-terminus that begins between amino acid numbers 81 and 139 of SEQ ID NO:4. Applicants have added claim 42, which depends from claim 41, and recites that the TRELL polypeptide comprises amino acid numbers 81 to 284 of SEQ ID NO:4.

Support for amended claims 1, 4 and 7 and for claims 40-42 may be found, for example, at page 11, lines 1-25; page 16, lines 3-16; page 27, line 4-page 31, line 3; page 33, line 24-page 34, line 9; and pages 36-37.

Claim 28 has been amended to recite a method of expressing a TRELL polypeptide in an animal cell culture

comprising: a) introducing a vector comprising a nucleic acid molecule having consecutive nucleotides that encode said TRELL polypeptide into said cell culture, wherein said TRELL polypeptide comprises the amino acid sequence of SEQ ID NO:4, or a soluble fragment thereof; and b) allowing said cell culture to live under conditions wherein said nucleic acid molecule is expressed in said cell culture.

Claim 30, which depends from claim 28, has been amended to recite that the animal cell culture is an insect cell culture or a mammalian cell culture. Claim 31, which depends from claim 28, has been amended to recite that the vector is a virus or a plasmid. Applicants have added claim 43, which depends from claim 30 and recites that the mammalian cell culture is a human cell culture.

Applicants have added claim 44, which recites a method of expressing a TRELL polypeptide in an animal cell culture, comprising the steps of: a) introducing a vector comprising a nucleic acid molecule comprising consecutive nucleotides encoding a TRELL polypeptide into said cell culture, wherein said TRELL polypeptide consists essentially of the amino acid sequence of SEQ ID NO:2; and b) allowing said cell culture to live under conditions wherein said nucleic acid molecule is expressed in said cell culture.

Applicants have added claim 45, which depends from claim 44, and recites that the animal cell culture is an insect cell culture or a mammalian cell culture. Applicants have added claim 46, which depends from claim 8, which recites that the host cell is a mammalian cell. Applicants have added claim

47, which depends from claim 46, and recites that the mammalian cell is a human cell.

Support for amended claims 28, 30 and 31 and for claims 43-47 may be found, for example, at page 7, lines 28-30; page 11, line 31-page 13, line 15; page 14, lines 11-29; page 16, lines 3-16; page 26, lines 8-11; page 32, lines 13-30; page 34, line 24-page 36, line 10.

The amendments and added claims presented herein do not constitute new matter. In sum, claims 1-4, 6-8, 10, 28, 30-31 and 39-47 are pending.

THE REJECTIONS

Claims 1, 4-8, 10, 28, 30, 31 and 36-38 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants traverse. The rejection of claims 5 and 36-38 has been rendered moot by their cancellation herein. Furthermore, the amended claims are in full compliance with 35 U.S.C. § 112.

New Matter

Claim 4 stands rejected for allegedly introducing new matter. The Examiner contends that the specification fails to provide literal support for the recitation "nucleic acid encoding a polypeptide comprising a portion that is at least 50% identical with amino acids 81-284 of SEQ ID NO:4." This rejection is rendered moot by amendment to claim 4, which no

longer includes the objected-to recitation.

Claim 5 stands rejected for allegedly introducing new matter. The Examiner contends that the specification fails to provide support for the particular combination of limitations required by the claim. This rejection is rendered moot by the cancellation of claim 5 herein.

Written Description

Claims 1, 4-8, 10, 28-31 and 36-38 stand rejected under 35 U.S.C. § 112 for allegedly lacking written description. The Examiner contends that these claims "embrace a full-length cDNA encoding a polypeptide comprising SEQ ID NO:2, but the specification fails to adequately describe such a molecule". At page 14 of the Office Action, the Examiner also states that "[t]his portion of the rejection can be overcome by amending claims to comprising nucleic acids 'consisting essentially of nucleic acids encoding SEQ ID NO:2.' The existing 'comprising' language is acceptable with reference to nucleic acids encoding SEQ ID NO:4…."

With respect to claims 5 and 36-38, the Examiner's rejection is rendered moot by their cancellation herein. The claims pending as of this amendment, *i.e.*, claims 1-4, 6-8, 10, 28, 30-31, and 39-47, either (1) do not recite SEQ ID NOS:1 or 2, or (2) recite nucleic acids or polypeptides that consist essentially of SEQ ID NOS:1 or 2, respectively. Thus, because the Examiner's contention has been rendered moot.

With respect to claim 4, the Examiner also asserts lack of written description because it is "drawn to substantially purified DNA that hybridizes to any fragment of

at least 20 consecutive bases [of] SEQ ID NOS:1 or 3, wherein the DNA encodes a polypeptide at least 50% homologous with amino acids 81-284 of SEQ ID NO:4." Because claim 4, as amended, no longer includes this recitation, the Examiner's contention is moot.

With respect to claim 5, the Examiner states that it is drawn to a substantially purified DNA that encodes the amino acid sequence of SEQ ID NO:2 OR 4, but which must encode alterations, deletions, or substitutions of these sequences that do not prevent binding of the polypeptides to cells that bind SEQ ID NOS:2 OR 4. The rejection of claim 5 is rendered moot by its cancellation herein.

Enablement

Claims 4, 5, and 28-31 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement for nucleic acid molecules encoding variants of SEQ ID NOS:2 or 4 which do not comprise exactly the same amino acid sequences as SEQ ID NOS:2 or 4, or for methods of expressing any TRELL polypeptide in a mammalian cell *in vivo*. Applicants traverse. As discussed below, amended claims 4 and 28-31 are fully enabled by the specification, and the rejection of claim 5 has been rendered moot by its cancellation herein.

The Examiner states that claim 4 is drawn to nucleic acids encoding variants of the polypeptides of SEQ ID NOS:2 and 4. The Examiner cites the language of claim 4 that requires "a polypeptide that is at least 50% homologous with amino acids 81-284 of SEQ ID NO:4." As amended, claim 4 no longer recites the language cited by the Examiner and thus the rejection is

obviated.

Applicants note that claim 4 has been amended to recite nucleic acids which encode a TRELL polypeptide of SEQ ID NO:4, or a soluble fragment thereof. Soluble TRELL polypeptide fragments are amply supported in the specification. For instance, the specification teaches a person of skill in the art at page 16 that "to create a soluble secreted form of TRELL, one would remove at the DNA level the N-terminus transmembrane regions, and some portion of the stalk region, and replace them with a type I leader or alternatively a type II leader sequence.... For example, the constructs containing all possible stalk lengths, *i.e.*, N-terminal truncations, could be prepared such that proteins starting at amino acids 81-139 would result." Furthermore, Example 2 discloses how applicants expressed a soluble, human TRELL polypeptide in both insect cells and human EBNA-293 cells. Thus, consistent with the Examiner's comments at page 10 of the instant Office Action, the specification fully enables a person of skill in the art to make soluble TRELL polypeptides.

Applicants further note that claim 4 has been amended to recite that claimed TRELL polypeptide, or a soluble fragment thereof, has the biological activity of being capable of binding to those cells provided in a Markush group supported by Table II on page 37. The Examiner asserts that "it is unclear if [a soluble TRELL polypeptide] has any TRELL biological activity." The Examiner further asserts that "the specification teaches only two forms of TRELL which can be considered to be functional, SEQ ID NOS:2 and 4." Applicants disagree.

While applicants agree that the application teaches a person of skill how to make and use functional TRELL polypeptides having the sequences of SEQ ID NOS:2 and 4, the specification also teaches how to make and use functional soluble human TRELL polypeptides. For example, on pages 34-35, the specification teaches how to make a functional soluble human TRELL polypeptide in both insect and human EBNA-293 cells. In the latter case, *secreted* TRELL is analyzed by immunoprecipitation with rabbit polyclonal anti-human TRELL antibodies.

Moreover, the application teaches that the cytotoxicity assays described on pages 36-37 were carried out according to Browning and Ribolini, *J. Immunol.* 143:1859-1867 (1989), attached hereto as Exhibit B. Browning and Ribolini teach, *inter alia*, functional assays of TNF and the TNF family member LT, wherein these molecules are added to cell cultures which were then analyzed for their cytotoxic and cell growth effects. *See*, Exhibit B, Table 1 and Figures 3-4. Furthermore, the binding of TNF and LT molecules to cells was analyzed. *See*, Exhibit B, Tables 2-3 and Figures 5-6.

Similar to the *Browning and Ribolini* article, Example 2 of the instant specification teaches at pages 36-37 cytoxicity and binding assays with a soluble TRELL polypeptide. The Examiner queries whether the modified, *i.e.*, soluble, human TRELL or the wild type human TRELL was used in the assay. Applicants submit that it is apparent from the example that a soluble TRELL polypeptide was used because that is the method disclosed by *Browning and Ribolini* and because sequence analysis indicates that the full-length TRELL polypeptide is a

membrane protein. *See*, specification at Figures 2a, 2b, and pages 14-16. Thus, the specification fully supports amended claim 4, as well as claims 41 and 42, which depend therefrom.

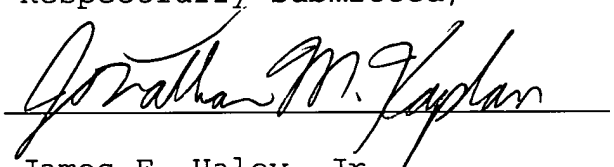
Claims 28, 30 and 31 stand rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner contends that "the specification is non-enabling for gene therapy protocols as the specification does not disclose methods by which the skilled artisan could predictably and reproducibly introduce and express TRELL polynucleotides in a mammal for therapeutic effect of any disease or disorder." The Examiner also states that "[t]his portion of the rejection may be overcome by limiting claims 28-31 to methods of expressing TRELL in a mammalian cell *in vitro*."

In order to expedite allowance of subject matter in this application, applicants have amended claims 28, 30 and 31 to recite methods of expressing a TRELL polypeptide in an animal cell culture, thus obviating the Examiner's rejection. These claim amendments are without prejudice to applicants' right to pursue subject matter relating to in vivo expression of TRELL polypeptides in a future application claiming priority herefrom under 35 U.S.C. § 120.

CONCLUSIONS

For the foregoing reasons, applicants believe the claims are in condition for allowance and respectfully request that this application be passed to issue.

Respectfully submitted,



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